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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,737	09/04/2003	Robert Gordon Webster	SJ-02-0016	1716

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EXAMINER

MCGAW, MICHAEL M

ART UNIT PAPER NUMBER

1648

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/654,737

Applicant(s)

WEBSTER ET AL.

Examiner

Michael M. McGaw

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 21 is/are rejected.
- 7) ☒ Claim(s) 2-12, 19 and 20 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>06 October 2003</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Objections

1. Claims 2-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 refers to the NS gene from A/England/1/53 influenza strain. The NS gene presumably has a defined sequence. Any other sequence is no longer the NS gene from A/England/1/53 influenza strain. Thus, modifications/changes to the sequence, such as deletions or substitutions, effect to remove a limitation, namely "the NS gene from A/England/1/53 influenza strain", from the independent parent claim.

2. Claims 19 and 20 are objected to because of the following informalities: These claims are dependent upon rejected claim 18. Appropriate correction is required.

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a reassortant virus, does not reasonably provide enablement for a method for producing a high titer reassortant virus. The specification does not enable any person skilled in the art to which it

Art Unit: 1648

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that on page 18 of the specification Applicant indicates that "there was no significant difference in peak titers" between PR8/Eng-NS and the parental strain A/PuertoRico/8/34, though there was a significant difference in the time to that peak. Thus, relative to the A/PuertoRico/8/34 strain from which the PR8/Eng-NS was derived, it does not appear that PR8/Eng-NS was "high titer".

Moreover, it was stated that this is an adapted strain. Presumably this means that the phenotype of "high titer" arose through successive passages. Such an adaptation arose as a result of sequence changes relative to the parent strain. Thus, it would follow that a reassortant strain using the NS gene from A/England/1/53 would not exhibit the "high growth" phenotype.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "high titer" in claim 1 is a relative term which renders the claim indefinite. The term "high titer" is not defined by the claim, the specification does not

Art Unit: 1648

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The Examiner was unable to find a definition for the term "high titer" in the specification. Clearly it is a relative term. It is not so clear as to what it is relative to. In the interest of compact prosecution the Examiner is interpreting the term relative to the strain from which the reassortant was derived, namely A/PR/8/34.

2. Claim 10 refers to "cells approved for use in humans." It sounds as though the cells are going to be administered in an *in vivo* method. Does Applicant mean cells approved for preparing vaccines for use in humans?

3. Claim 14 refers to "the HA and NA genes from an influenza virus of interest..." It is not clear whether this includes or excludes the HA and NA genes from A/England/1/53. If it includes the HA and NA genes from A/England/1/53, then it reads on the work of Govorkova.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13, 15, 17, 18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Govorkova, E.A. et al. (1999) *The Journal of Infectious Diseases* (cited by Applicant).

Applicant claims "A reassortant influenza virus strain comprising a modified A/PuertoRico/8/34 influenza strain, wherein the NS gene of the A/PuertoRico/8/34 influenza strain is replaced with the NS gene from the A/Eng1and/1/53 influenza strain and the HA and NA genes from an influenza virus strain of interest.

Govorkova, E.A. et al. (1999) ("Govorkova") teach a Vero-cell adapted reassortant influenza strain with high growth properties and high production of protein. The reassortant was created from the parental strains of A/England/1/53 and A/PuertoRico/8/34. Govorkova reported that their "high growth" strain "was genotyped by partial sequence analysis of each gene segment; the surface proteins originated from A/England/1/53 (H1N1) and the six 'internal' gene segment from A/PR/8/34 (H1N1)" (See page 250, col. 2, last paragraph) Govorkova indicates on page 252 that, at least at that time, high growth potential was associated with the M gene. The authors appeared to be surprised that the M gene came from the A/PuertoRico/8/34 strain as the parental strain exhibited poor replication properties. (See paragraph straddling pages 251-252) The authors then conclude that based on their results "the HA gene appears to play a leading role in the adaptability." Govorkova noted the increased yield in viral protein production achieved with the reassortant virus.

Applicant reports:

Contrary to what was reported in the Govorkova et al. manuscript, sequence analysis of the complete genome of A/England/1/53/v-a showed that this high-yielding virus contained not only the H/A and NA genes from A/England/1/53, but also the NS gene from this same strain. The remaining A/England/1/53/v-a proteins (PB2, PB1, PA, MP and M) had more than 99% nucleotide identity to those of A/PuertoRico/8/34. The NS gene from A/England/1/53/v-a had only 90% identity to the corresponding A/PuertoRico/8/34 gene, the HA gene had 98% identity and the NA gene 97%

Art Unit: 1648

identity. Therefore, the greatest number of genetic changes between A/England/1/53/v-a and A/PuertoRico/8/34 was in the NS gene.

Thus, Applicant states that Govorkova was in possession of the product that Applicant is now claiming, namely a reassortant influenza virus where the NS gene of A/PuertoRico/8/34 is replaced by the NS gene of A/England/1/53. Govorkova's possession predates Applicant's claim by eight years, thus qualifying as a prior art reference under 35 U.S.C. 102(b).

The Examiner is relying, in part, on MPEP 2112 to arrive at a conclusion of anticipation. MPEP 2112 provides:

The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Thus, Govorkova inherently discloses the composition that Applicant now claims.

Moreover, MPEP 2112 states:

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

As to the claims directed to the compositions, the Govorkova reference anticipates Applicant's claimed composition even though Govorkova did not appreciate what was

Art Unit: 1648

possessed at the time due to the fact that Govorkova had not fully characterized that which was possessed. As to the specifics of claims 16, 17 and 18, Govorkova's work was performed in the context of influenza virus vaccine production thus anticipating claims directed to vaccines, master strains and kits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Govorkova et al.

Claim 16 is directed at a vaccine further comprising an adjuvant. As Applicant admits on page 12, line 5, it is known to use adjuvants with influenza vaccines to enhance the immune response. One of ordinary skill in the art would have been motivated to add an adjuvant to boost the immune response. One of ordinary skill in the art would have expected an enhanced immunological effect because the use and effectiveness of adjuvants with influenza vaccines is known. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claim 14 has been rejected above under 35 USC §112, ¶2 due to the language “the HA and NA genes of a virus of interest.” It appears that Applicant intended to exclude the HA and NA genes from A/England/1/53 by virtue of this statement, though it is not completely clear.

The closest prior art is Egorov, A. et al. teaching influenza reassortants using an NS1 gene product with deletions in the sequence derived from A/Leningrad/134/57 strain influenza virus and the remaining gene segments from A/PuertoRico/8/34. Egorov, A. et al. report that these reassortants produce high titers in Vero cells. (See abstract) One of ordinary skill in the art would recognize that reassortants containing HA and NA genes of a virus of interest could be created using a variety of techniques such as the various reverse genetics systems as taught by Hoffman, E. et al., (2002), Neumann, G. et al. (1999), Palese, P. et al (1996), etc.

While Govorkova was in possession of the composition claimed by Applicant, this does not anticipate or render obvious methods of using derivatives of the NS gene of A/England/1/53 in combination with HA and NA of an influenza virus of interest in combination with the remaining 5 gene segments from A/PuertoRico/8/34. This statement is based upon the fact that Govorkova stated explicitly that their Vero-adapted high growth A/England/1/53 strain contained the two gene segment encoding the surface proteins from A/England/1/53 and the six “internal gene segments from A/PR/8/34. The application of such a strain for the further development of vaccine would be limited as the HA gene, which Govorkova indicated was responsible for the

Art Unit: 1648

phenotype, would have to be switched for another HA gene for vaccine, presumably resulting in a loss of the disclosed desirable replication phenotype. Thus, Govorkova does not teach or suggest using a modified NS gene derived from the A/England/1/53 strain even though that was ultimately determined to be what was possessed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

U.S. Patent Nos. 5,824,536 and 6,344,354 B1 to Webster et al. teaching reassortant influenza virus composed of the HA and NA segments of A/England/1/53 and the remaining 6 segments of Puerto Rico. The patent teaches growth to high titer by the Vero-cell line-adapted reassortant. The work largely parallels that of Govorkova discussed above.

Talon, J. et al. (Apr. 2000) *Proc. Natl. Acad. Sci.* ("Talon") teach the generation of influenza A and B virus vaccines using reverse genetics approaches employing virus encoding altered NS1 proteins. One of the critical benefits of employing such a technique, according to Talon, is the loss of interferon antagonist activity achieved by the truncated NS1 protein, thereby enhancing the immune response. Talon also reports that viruses expressing altered NS1 proteins show significant growth attenuation in embryonated eggs and mice. (See page 4309 and 4313, col. 2).

Schickli, J.H. et al. Plasmid-only Rescue of influenza A virus vaccine candidates (2001) *Phil. Trans. R. Soc. Lond.* 356(1416):1965-73. Schickli, J.H. et al. discuss

Art Unit: 1648

reverse genetics-based approaches for vaccination against influenza viruses. One of the strategies discussed involved the creation of master strains containing mutated NS1 proteins. (See page 1966)

See form 892 for a listing of additional pertinent art.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

m.m.

Michael M. McGaw
Friday, January 21, 2005


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1/24/05